

WHAT IS CLAIMED IS:

1. A microcapsule for culturing anchorage-dependent cells comprising an inner extracellular matrix surrounding the cells and an outer shell of synthetic polymer surrounding and supporting the extracellular matrix; wherein said microcapsule is permeable to nutrients necessary to sustain normal metabolic functions of the cells and to toxins released by the cells; and wherein said outer shell has a thickness of from about 1 to about 20 μm .
2. The microcapsule of claim 1 wherein said inner extracellular matrix comprises a biopolymer inner layer and a biocompatible synthetic polyelectrolyte outer layer, wherein said inner layer and said outer layer have charges sufficient to form a complex of said biopolymer and said polyelectrolyte.
3. The microcapsule of claim 2 wherein said outer shell comprises (i) a biopolymer selected from the group consisting of cationic collagen modified to have a pKi of at least about 9, anionic esterified hyaluronic acid, anionic amine-modified hyaluronic acid, fibronectin, and laminin, and (ii) a biocompatible synthetic polyelectrolyte having an electrolytic charge opposite to that of the biopolymer.
4. The microcapsule of claim 3 wherein said biocompatible synthetic polyelectrolyte of said outer shell comprises an acrylate ter-polymer of methacrylic acid, hydroxyethyl methacrylate, and methyl methacrylate.
5. A microcapsule for culturing anchorage-dependent cells comprising an inner extracellular matrix surrounding the cells and an outer shell surrounding and supporting the extracellular matrix; wherein said microcapsule is permeable to nutrients necessary to sustain normal metabolic functions of the cells and to toxins released by the cells; and wherein said outer shell comprises a macro-porous exoskeleton formed by complex coacervation with said extracellular matrix.

6. The microcapsule of claim 5 wherein said macro-porous exoskeleton comprises at least one of alumina, alumina sol, and chitosan.

7. A microcapsule for culturing anchorage-dependent cells comprising an inner extracellular matrix surrounding the cells, a macro-porous exoskeleton surrounding and supporting the extracellular matrix; and an outer shell of synthetic polymer surrounding the macro-porous exoskeleton; wherein said microcapsule is permeable to nutrients necessary to sustain normal metabolic functions of the cells and to toxins released by the cells; and wherein said outer shell has a thickness of from about 1 to about 20 μm .

8. The microcapsule of claim 7 wherein said inner extracellular matrix comprises a biopolymer inner layer and a biocompatible synthetic polyelectrolyte outer layer, wherein said inner layer and said outer layer have charges sufficient to form a complex of said biopolymer and said polyelectrolyte.

9. The microcapsule of claim 7 wherein said macro-porous exoskeleton comprises at least one of alumina, alumina sol, and chitosan.

10. The microcapsule of claim 7 wherein said synthetic polymer of said outer shell comprises an acrylate ter-polymer of methacrylic acid, hydroxyethyl methacrylate, and methyl methacrylate.

11. A method of preparing a microcapsule having anchorage-dependent cells surrounded by an inner extracellular matrix and an outer shell of synthetic polymer surrounding and supporting the extracellular matrix, the process comprising:

preparing an inner extracellular matrix having an inner layer and an outer layer, comprising extruding an inner layer biopolymer solution containing bioactive cells into a biocompatible synthetic polyelectrolyte outer layer; wherein said inner layer and said outer layer have charges sufficient to form a complex of said biopolymer and said polyelectrolyte; and

forming an outer shell by encapsulating said inner extracellular matrix containing said cells with a synthetic polymer solution, wherein said outer shell thus-formed has a thickness of from about 1 to about 20 μm .

12. The method of claim 11 wherein said synthetic polymer solution of said outer shell comprises (i) a biopolymer selected from the group consisting of cationic collagen modified to have a pK_i of at least about 9, anionic esterified hyaluronic acid, anionic amine-modified hyaluronic acid, fibronectin, and laminin, and (ii) a biocompatible synthetic polyelectrolyte having an electrolytic charge opposite to that of the biopolymer.

13. The method of claim 12 wherein said biocompatible synthetic polyelectrolyte of said outer shell comprises an acrylate ter-polymer of methacrylic acid, hydroxyethyl methacrylate, and methyl methacrylate.

14. A method of preparing a microcapsule having anchorage-dependent cells surrounded by an inner extracellular matrix and a macro-porous exoskeleton surrounding and supporting the extracellular matrix, the process comprising:

preparing an inner extracellular matrix having an inner layer and an outer layer, comprising extruding an inner layer biopolymer solution containing bioactive cells into a biocompatible synthetic polyelectrolyte outer layer; wherein said inner layer and said outer layer have charges sufficient to form a complex of said biopolymer and said polyelectrolyte; and

suspending said inner extracellular matrix containing said cells in an exoskeleton material having a charge opposite to that of the outer layer of said extracellular matrix to form a macro-porous exoskeleton over said extracellular matrix.

15. The method of claim 14 wherein said macro-porous exoskeleton comprises at least one of alumina, alumina sol, and chitosan.

16. The method of claim 14 further comprising forming an outer shell by encapsulating the microcapsule in a synthetic polymer solution.
17. The method of claim 16 wherein said synthetic polymer solution comprises an acrylate ter-polymer of methacrylic acid, hydroxyethyl methacrylate, and methyl methacrylate.
18. A method of culturing anchorage-dependent cells comprising applying agitation to the microcapsule of claim 1 after a predetermined time to rupture the outer shell, and removing the extracellular matrix to recover the cells.
19. A multi-layer microcapsule comprising bioactive cells attached to a microcapsule membrane; wherein said microcapsule membrane comprises (i) a first inner layer of biopolymer selected from the group consisting of cationic collagen, anionic collagen, anionic esterified hyaluronic acid, anionic amine-modified hyaluronic acid, fibronectin, and laminin; (ii) a second intermediate layer of polyelectrolyte synthetic polymer; and (iii) a third outer layer forming an exoskeleton to provide mechanical stability; wherein said first inner layer and said second intermediate layer are complexed via ionic charges; wherein said second intermediate layer and said third outer layer are complexed via ionic charges; wherein said microcapsule membrane is permeable to molecules smaller than or equal to the size of albumin, to nutrients necessary to sustain normal metabolic functions of the bioactive cells, and to toxins released by the bioactive cells; and wherein said microcapsule membrane is impermeable to immunoglobulins and macrophages.
20. The multi-layer microcapsule of claim 19 further comprising (iv) a fourth outer layer comprising a polyelectrolyte synthetic polymer surrounding said third layer, wherein said fourth outer layer is complexed with said third layer via ionic charges.

21. The multi-layer microcapsule of claim 19 wherein said second intermediate layer of polyelectrolyte synthetic polymer is an acrylate ter-polymer of methacrylic acid, hydroxyethyl methacrylate, and methyl methacrylate.

22. The multi-layer microcapsule of claim 19 wherein said third outer layer comprises a material selected from the group consisting of alumina, alumina sol, and chitosan.

23. The multi-layer microcapsule of claim 19 wherein said bioactive cells comprise a mixture of dividing cells and non-dividing cells.

24. The multi-layer microcapsule of claim 23 wherein said bioactive cells comprise a mixture of hepatocyte cells and non-parenchymal cells.

25. The multi-layer microcapsule of claim 4 wherein said third layer comprises a ceramic sol modified to be negatively charged, wherein said third layer is unstable at a physiological pH of 7.4 to provide a short-term controlled release of cells, cell aggregates, or tissue structures.

26. A process of preparing a bioartificial liver assist device comprising packing one or more of the biocompatible microcapsule of claim 1 in a bioreactor.

27. A process of preparing a bioartificial liver assist device comprising packing one or more of the biocompatible microcapsule of claim 5 in a bioreactor.

28. A process of preparing a bioartificial liver assist device comprising packing one or more of the biocompatible microcapsule of claim 7 in a bioreactor.

29. A bioartificial liver assist device comprising one or more of the biocompatible microcapsule of claim 1 contained within a bioreactor.

30. A bioartificial liver assist device comprising one or more of the biocompatible microcapsule of claim 5 contained within a bioreactor.

31. A bioartificial liver assist device comprising one or more of the biocompatible microcapsule of claim 7 contained within a bioreactor.

32. A method of preparing living cells for multi-dimensional imaging to study cells, tissue, or tissue constructs, the method comprising culturing at least one cell in the microcapsule of claim 1 and imaging the cell using microscopy.

33. A method of preparing living cells for transplantation comprising culturing at least one cell in the microcapsule of claim 1, harvesting the cell, and coupling the cell to a scaffold.

34. A method of analyzing cells comprising removing at least one cell from a biopsy sample, culturing the cell in the microcapsule of claim 1, and performing cytometry analysis.